American Journal of Medical Genetics 70:52–57 (1997)

The Marshall Syndrome: Report of a New Family and Review of the Literature

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The Marshall syndrome is an autosomal dominant trait comprising ocular abnormalities, sensorineural hearing loss, craniofacial anomalies, and anhidrotic ectodermal dysplasia. To our knowledge, only seven additional multigenerational families have been reported since the initial description of the disorder by Marshall in 1958. We present a family in which six members in four generations are affected with apparent Marshall syndrome. We also review and compare similar disorders, such as Stickler, Weissenbacher-Zweimüller, and Wagner syndromes, and conclude that Marshall syndrome is a distinct entity. Am. J. Med. Genet. 70:52–57, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: Marshall syndrome; Stickler syndrome; Weissenbacher-Zweymüller syndrome; Wagner syndrome; type II collagen; ectodermal dysplasia

INTRODUCTION

In 1958, Marshall described seven members in three generations of a family who were affected with a form of hereditary "ectodermal dysplasia" comprising ocular abnormalities, minor facial anomalies, and hearing loss [Marshall, 1958]. In this publication, the author emphasized the ectodermal abnormalities, including defects in sweating and dental structures, and the ophthalmologic abnormalities, including ocular hypertelorism, myopia, and congenital or juvenile cataracts.

Since publication of Marshall's articles, only seven additional families have been described [Ruppert et al., 1970; Keith et al., 1972; Zellweger et al., 1974; O'Donnell et al., 1976; Winter et al., 1983; Nguyen et al., 1988; and Stratton et al., 1991], and the phenotype has been expanded to include: short stature; flat or retruded midface with short, depressed nose, flat nasal bridge and anteverted nares; cleft palate with or without the Pierre Robin sequence; appearance of large eyes with ocular hypertelorism; cataracts, either congenital or juvenile; esotropia; high myopia; sensorineural hearing loss; spondyloepiphyseal abnormalities; calcification of the falx cerebri; ectodermal dysplasia; and autosomal dominant inheritance. The sparsity of additional reports suggests that Marshall syndrome (MS) is a rare disorder.

The Stickler syndrome (SS) is a much more common autosomal dominant trait comprising Pierre Robin sequence, midfacial hypoplasia, high myopia, sensorineural hearing loss, and a mild spondyloepiphyseal dysplasia that may lead to short stature and premature arthritis [Herrmann et al., 1975]. Because MS and SS are similar, it was suggested by Cohen in 1974 that these two entities may actually be variable expressions of the same disorder. In the years since Cohen's letter, a debate has occurred between those who think that MS and SS represent the same entity [Baraitser, 1982; Winter et al., 1983] and those who believe that MS and SS are two discrete syndromes [Zellweger, 1975; O'Donnell et al., 1976; Ayme and Preus, 1984; Stratton et al., 1991].

The debate surrounding the existence of MS has spread to two additional syndromes with some degree of overlap. Wagner syndrome (WS) combines ophthalmologic abnormalities (high myopia, hyaloideoretinal degeneration, retinal detachment, cataracts, and shallow orbits) with a broad, sunken nasal bridge, micrognathia with or without a cleft palate, and non-specific skeletal anomalies [Wagner, 1938; Liberfarb et al., 1981]. The Weissenbacher-Zweymüller syndrome (W-ZS), first described in 1964 as "Pierre-Robin syndrome with fetal chondrodysplasia," combines neonatal micrognathia, rhizomelic shortness of the limbs, vertebral clefts, dumbbell-shaped femora and humeri, midface hypoplasia, and myopia with optic nerve hypoplasia. [Weissenbacher-Zweymüller, 1964; Haller et al., 1975; Winter et al., 1983]. The manifestations of these four entities are described in Table I.

Patients with MS have two major anomalies not

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Received 27 February 1996; Accepted 30 August 1996

TABLE I. Manifestations of Marshall (MS), Stickler (SS), Wagner (WS) and Weissenbacher-Zweymüller (W-ZS) Syndromes

Findings	MS	SS	WS	W-ZS
Head	Brachycephaly, thick calvaria	Normocephaly	Normocephaly	Flat occiput
Midface	Flat, retracted	Dish shaped, flat	Hypoplastic with epicanthi	Maxillary hypoplasia
Nose	Small short saddle nose with flat bridge	Long nose with prominent nasal bridge	Broad sunken nasal bridge	Depressed nasal bridge
Ocular hypertelorism	Yes, with shallow orbits	No	No	Yes
Other ocular findings	High myopia, glaucoma, esotropia, retinal detachment, no astigmatism	High myopia, vitreoretinal degeneration/ detachment, astigmatism	Hyaloideoretinal degeneration, retinal detachment	Myopia, optic nerve hypoplasia, glaucoma
Cataracts	Frequent, congenital	Occasional	Early onset	No
Hearing loss	Frequent, sensorineural	Mild	No	Yes
Cleft palate +/– Pierre-Robin malformation	Occasional	Common	Yes	Yes
Ectodermal dysplasia	Yes	No	No	No
Stature	Short and stocky	Normal or tall and thin	Short stature	Early short stature, catch-up growth
Skeletal abnormalities	Spondylo-epiphyseal abnormalities	Osteochondro-dysplasia, spon-dyloepiphyseal dysplasia	Genu valgum	Rhizomelic chon-drodysplasia, neural tube defect
Joints	Hypoextensible	Hyperextensible, arthropathy with degenerative arthritis	No arthropathy	Myopia, optic nerve hypoplasia, glaucoma
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive
COL2A1 mutation	No	Yes	Yes	?

shared with any of these other disorders: ectodermal dysplasia and ocular hypertelorism. We have had the opportunity to study a family with six affected individuals in four generations in whom these two traits predominated.

CLINICAL REPORTS

Patient 1

EM, the proposita (III-2, Fig. 1), a 17-year-old black woman, was seen at the age of 2 years because of marked ocular hypertelorism, dystopia canthorum, midface hypoplasia with a flat nasal bridge and anteverted nares. Her scalp hair, which had never been cut, was very sparse, as were her eyebrows and eyelashes; her teeth and nails were normal, and no problems were noted with sweating. Karotype was normal (46,XX). Because of her appearance, and its similarity to that of her mother, a tentative diagnosis of MS was made, and a work-up was scheduled.

Because of poor compliance, the work-up was never completed. At the age of 8, the proposita had some surgery on her eyes. At 11, she was placed in foster care and returned for evaluation and follow-up. At that time, her height was 133 cm (10th centile); her weight was 30.4 kg (15th centile); and her head circumference (OFC) was 51 cm (25th centile). She had striking ocular hypertelorism with an inner canthal distance of 40 mm (>>97th centile). There was midface hypoplasia with primary telecanthus, broad, flat nasal bridge, nasal hypoplasia, relative mandibular prognathism, and sparse scalp hair and eyebrows (Fig. 2a,b). Ophthalmologic examination revealed intermittent exotropia, myopia, and posterior embryotoxon.

Psychodevelopmental evaluation demonstrated low average intelligence and adjustment disorder. Audiologic testing, auditory evoked responses, skeletal survey, CT scan of the brain, and dermatoglyphic evaluation were all normal. Following this evaluation, the proposita underwent craniofacial reconstructive surgery for repair of hypertelorism, consisting of: orbital translocation; cranial bone graft; first-stage nasal reconstruction; medial canthopexy; and lateral canthopexy. As seen in Figure 3, this operation resulted in what the patient considered significant aesthetic improvement.

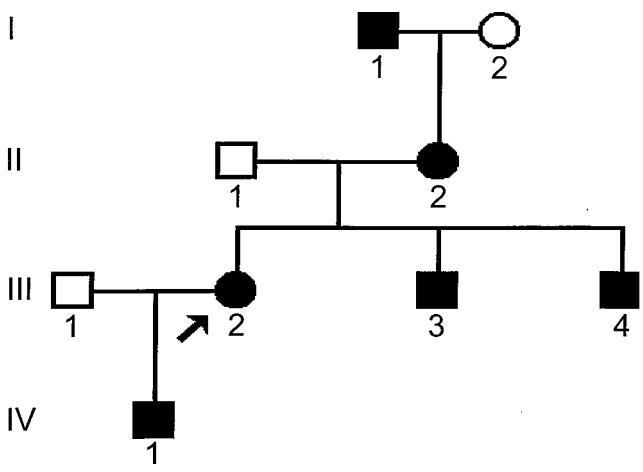

Fig. 1. Pedigree of family.

Fig. 2. **a:** Frontal and (**b**) profile views of patient 1 at age 11, prior to craniofacial surgery.

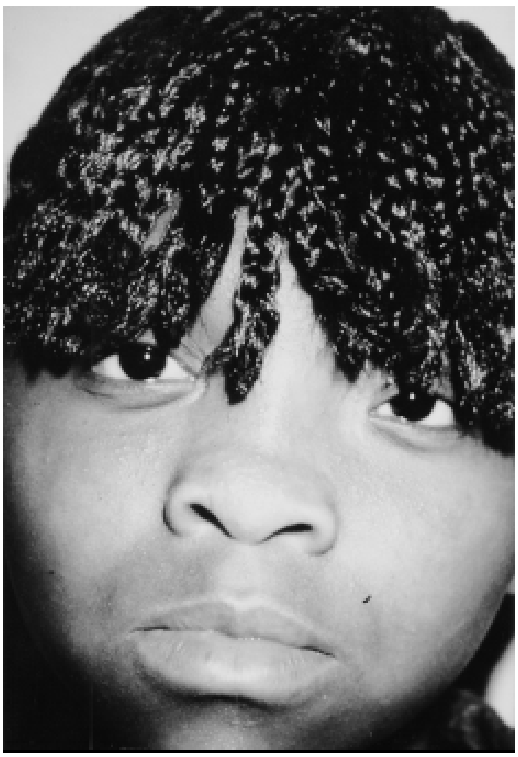

Fig. 3. Frontal view of patient 1 at age 15, following craniofacial surgery. Patient is wearing a wig.

At the age of 16 years the proposita became pregnant. She recently gave birth to an affected son (Patient 5, below).

Patient 2

FM, the 13-year-old brother of the proposita (III-3 in Fig. 1), was seen neonatally because of similarities in facial appearance to his older sister. At that time he was noted to have hypertelorism, midface hypoplasia with a flat nasal bridge, and a paucity of hair. He was not seen again until age 5 11/12. On physical exam at that time, his height, weight, and head circumference were all normal. He had more severe ocular hypertelorism than his sister, with an inner canthal distance of 44 mm (>>95th centile), and telecanthus. He had significant frontal recession, wide, flat nasal bridge, bimaxillary protrusion with mandibular prognathism, carious primary teeth with an anterior crossbite, and sparse scalp hair and eyebrows (Fig. 4). FM also had mild thoracolumbar scoliosis and bilateral cryptorchidism. Ophthalmologic examination showed decreased visual acuity due to uncorrected high myopia and amblyopia, and esotropia. A heart murmur was heard; evaluation documented mild tricuspid and pulmonic regurgitation. Psychoeducational evaluation showed developmental delay with functioning in the mildly retarded range and adjustment disorder. Audiologic testing, CT scan of the brain, skeletal survey, dermatoglyphics, and karyotype were all normal.

Following completion of the evaluation, FM, like his sister, underwent craniofacial reconstructive surgery for hypertelorism. Results of his surgery are shown in Figure 5.

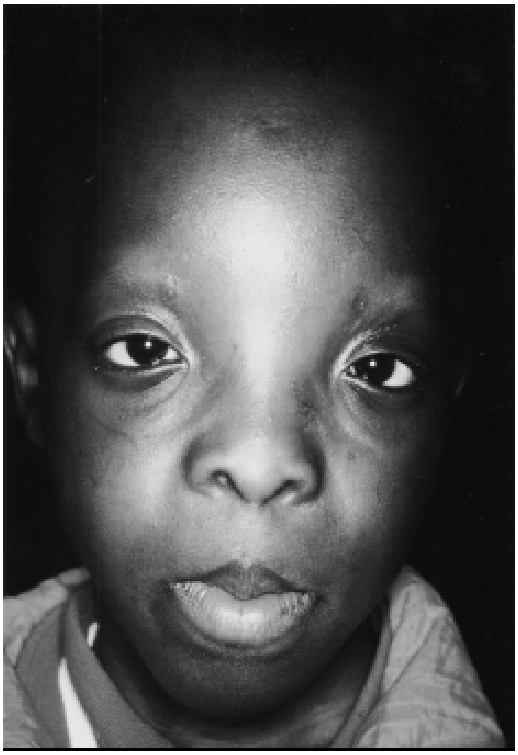

Fig. 4. Frontal view of patient 2 at age 9, prior to craniofacial surgery.

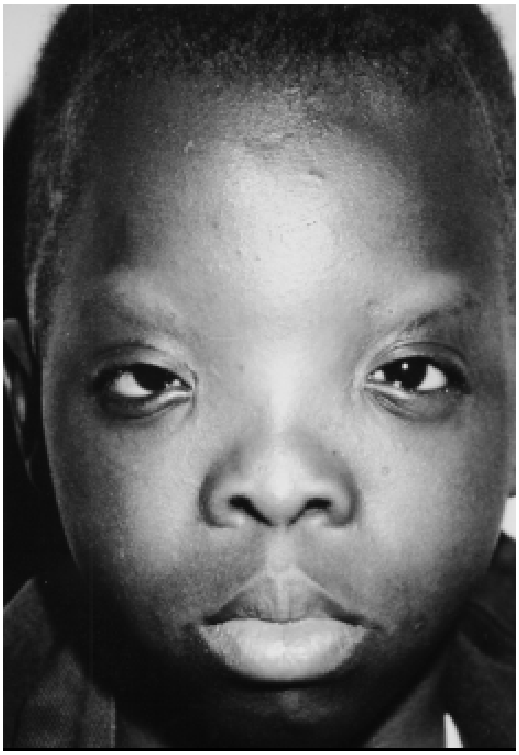

Fig. 5. Frontal view of patient 2 at age 11, following craniofacial surgery.

Patient 3

NM, the 9-year-old brother of EM (III-4 in Fig. 1), was first seen at 3 10/12 years because of findings similar to those of his older sibs. As shown in Figure 6, his facial anomalies, including hair pattern, are similar to those of EM and FM, but the hypertelorism is somewhat less severe. Like his brother, NM also had bilateral cryptorchidism. Ophthalmologic examination in NM revealed high myopia, decreased visual acuity, intermittent exotropia, and posterior embryotoxon. Psychoeducational testing showed normal intelligence and an adjustment disorder. Results of audiologic testing, CT scan of the brain, skeletal survey, dermatoglyphics, and karyotype were all normal.

NM, too, underwent craniofacial reconstructive surgery to repair his hypertelorism, with good cosmetic results (Fig. 7). Also, like his brother, he underwent orchidopexy.

Patient 4

Ms. M (II-2 in Fig. 1) is the 35-year-old mother of the children. She would not consent to examination but, as seen in Fig. 8, she had very similar craniofacial anomalies to those of her three children, including ocular hypertelorism, midfacial hypoplasia, telecanthus, and sparsity of scalp hair and eyebrows. Ms. M has a diagnosis of chronic schizophrenia. She has never had surgery to repair her hypertelorism.

Ms. M reports that her father had a similar facial appearance, and also had a paucity of scalp hair. Unfortunately, no photographs are available for study.

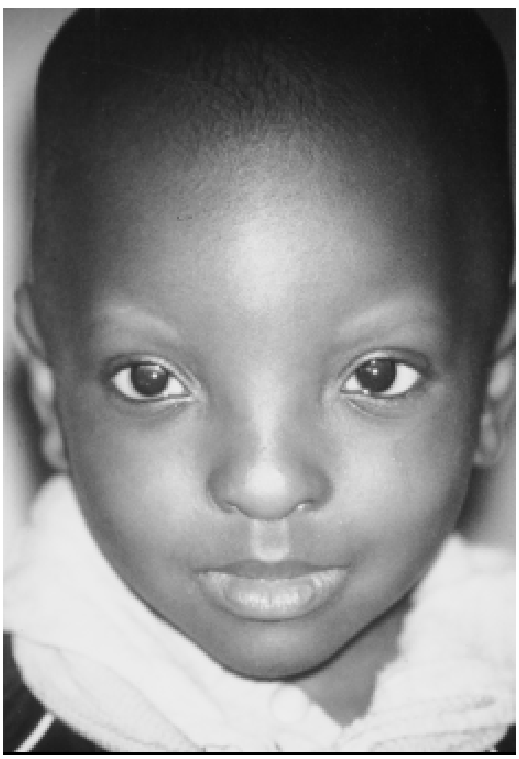

Fig. 6. Frontal view of patient 3 at age 4, prior to craniofacial surgery.

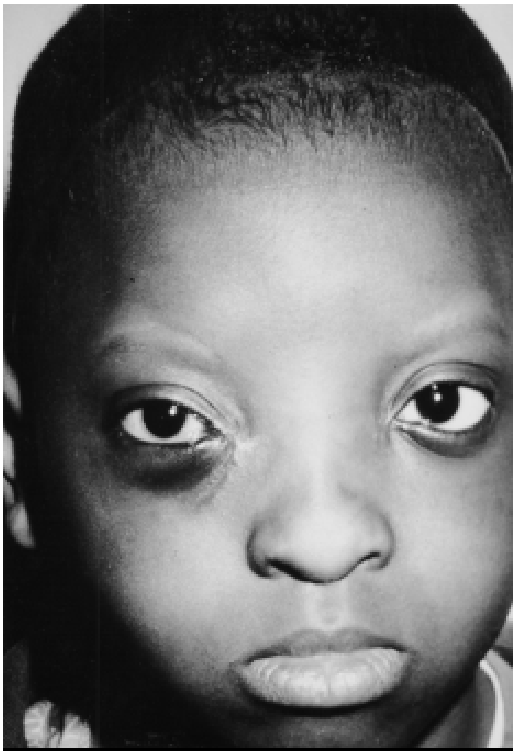

Fig. 7. Frontal view of patient 3 at age 7, following craniofacial surgery.

Patient 5

MJ (IV-1 in Fig. 1), the son of the proposita, is currently 2 months old. Neonatally he was noted to have ocular hypertelorism, midface hypoplasia, soft-tissue telecanthus, and sparse scalp hair. However, unlike his uncles, MJ did not have cryptorchidism.

DISCUSSION

The debate regarding whether MS, SS, WS, and W-ZS are actually separate entities, or represent variable expression of the same mutant gene, has been fueled by the fact that each of these disorders shares a number of common traits. Ophthalmologic abnormalities, including high myopia, midface hypoplasia, micrognathia with or without palatal clefting, and nonspecific skeletal abnormalities have been reported in all four of these entities. This overlap was the impetus that led Cohen in 1974 to suggest that MS and SS were not phenotypically unique entities. In 1982, Baraitser et al. suggested that the entity be called Marshall/Stickler syndrome, since Marshall's publication preceded Stickler's by nine years. In 1983, Winter et al. described three infants with W-ZS who later developed MS. On the basis of the natural history seen in these patients, these authors suggested that MS, SS, and W-ZS may, in fact, represent the same disorder.

But in spite of these overlaps, the fact that each of these entities has unique, distinctive manifestations cannot be overlooked. In his initial report, Marshall noted the presence of abnormalities of the ectodermal derivatives and actually described this disorder as an ectodermal dysplasia. Also, although not commented on by the author, the photograph of Marshall's patient No. 6 shows what appears to be striking ocular hypertelorism. Thus, these two traits appear to occur only in MS, and not in SS, WS, or W-ZS.

Objective rejection of the lumping of MS and SS was initially provided by Ayme and Preus in 1984, based upon a survey of published reports on 18 patients. These authors used cluster analysis of 53 separate characteristics. Tabulation of the scores obtained from these patients suggested that MS and SS are separate, dominantly inherited disorders, each of which shows variable expression.

Further evidence that MS and SS are distinct comes from the finding of Stratton et al. [1991] that no gross rearrangement in the type II collagen gene can be found in individuals with MS. Type II collagen is the major collagen component of cartilage and the vitreous humor. As such, COL2A1, the gene that codes for type

Fig. 8. Photo of family, including (left to right) patients 3, 1, 4, and 2.

II collagen, would be an important candidate gene for disorders that combine skeletal abnormalities with high myopia and vitreoretinal degeneration. In fact, in 1988 Francomano et al. found tight linkage to COL2A1 in five families with SS. Although genetic heterogeneity has been demonstrated in SS, with some SS families showing no linkage [Stratton, 1991], the fact that no defect in the COL2A1 gene can be identified in any patients with MS suggests that MS and SS are genetically separate.

REFERENCES

Ayme S, Preus M (1984): The Marshall and Stickler syndromes: Objective rejection of lumping. J Med Genet 21:34–38.

Baraitser M (1982): Marshall/Stickler syndrome. J Med Genet 19:139–140.

Cohen MM Jr (1974): The demise of the Marshall syndrome. J Pediatr 85:878.

Francomano CA, Liberfarb RM, Hirose T, Maumanee IH, Streeten EA, Myers DA, Pyeritz RE (1988): The Stickler syndrome is closely linked to COL2A1, the structural gene for type II collagen. Pathol Immunopathol Res 7:104–106.

Haller JO, Bendon WE, Robinow M, Slovis TL, Baker DH, Johnson GF (1975): The Weissenbacher-Zweymüller syndrome of micrognathia and rhizomelic chondrodysplasia at birth with subsequent normal growth. Am J Roent Rad Ther Nucl Med 125:936–943.

Herrmann J, France TD, Spranger JW, Opitz JM, Wiffler C (1975): The Stickler syndrome (hereditary arthroophthalmopathy). BD:OAS XI: 76–103.

Keith CG, Dobbs RH, Shaw DG, Cottrall K (1972): Abnormal facies, myopia, and short stature. Arch Dis Child 47:787–793.

Liberfarb RM, Hirose T, Holmes LB (1981): The Wagner-Stickler syndrome: A study of 22 families. J Pediatr 99:394–399.

Marshall D (1958): Ectodermal dysplasia: Report of a kindred with ocular deformities and hearing loss. Am J Ophthalmol 45:143–156.

Nguyen J, Philip N, Arnaud JP, Sibille G, Tisne C, James F (1988): Syndrome de Marshall. Arch Franz Pediatr 45:49–51.

O'Donnell JJ, Sirkin S, Hall, BD (1976): Generalized osseous abnormalities in the Marshall syndrome. BD:OAS XII:299–314.

Ruppert ES, Buerk E, Pfordresher MF (1970): Hereditary hearing loss with saddle nose and myopia. Arch Otolaryngol 92:95–98.

Stratton RF, Lee B, Ramirez F (1991): Marshall syndrome. Am J Med Genet 41:35–38.

Wagner H (1938): Ein bisher unbekanntes Erbleiden des Auges (degeneration-hyaloideo-retinalis hereditaria), beobachtet im Kanton Zurich. Klin Mbl Augenheilk 100:840–858.

Winter RM, Baraitser M, Laurence KM, Donnai D, Hall CM (1983): The Weissenbacher-Zweymüller, Stickler, and Marshall syndromes: Further evidence for their identity. Am J Med Genet 16:189–199.

Zellweger H, Smith JK, Grutzner P (1974): The Marshall syndrome: Report of a new family. J Pediatr 84:868–871.